

# A Review of Methods for Analysis of the Expected Value of Information

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*In recent years, value-of-information analysis has become more widespread in health economic evaluations, specifically as a tool to guide further research and perform probabilistic sensitivity analysis. This is partly due to methodological advancements allowing for the fast computation of a typical summary known as the expected value of partial perfect information (EVPPI). A recent review discussed some approximation methods for calculating the EVPPI, but as the research has been active over the intervening years, that review does not discuss some key estimation methods. Therefore, this paper presents a comprehensive review of these new methods. We begin by providing the*

*technical details of these computation methods. We then present two case studies in order to compare the estimation performance of these new methods. We conclude that a method based on nonparametric regression offers the best method for calculating the EVPPI in terms of accuracy, computational time, and ease of implementation. This means that the EVPPI can now be used practically in health economic evaluations, especially as all the methods are developed in parallel with R functions and a web app to aid practitioners. **Key words:** probabilistic sensitivity analysis; value of information; computation methods; EVPPI. (Med Decis Making 2017;37:747–758)*

Health economic models are used to predict the costs and health effects of competing health-care technologies. Input parameters for these models are informed by empirical evidence and are therefore rarely known with certainty. The typical method for assessing input uncertainty is probabilistic sensitivity analysis (PSA): that is, Monte Carlo (MC) or bootstrap sampling from the probability distributions of the input parameters coupled with model evaluation in order to generate samples of

predicted costs and effects. PSA is a fundamental component of any health economic evaluation and is recommended by health technology assessment (HTA) bodies such as the National Institute for Health and Care Excellence (NICE) in the UK,<sup>1</sup> across other countries in Europe,<sup>2</sup> and beyond.<sup>3,4</sup>

A fully decision-theoretic approach to PSA is based on the analysis of the *value of information* (VoI),<sup>5</sup> an increasingly popular method in health economic evaluation.<sup>6–15</sup> This paper focuses on VoI summary measures used to quantify the expected value of obtaining *perfect* information about the underlying model parameters. Because it is impossible to obtain perfect information, this analysis simply places an upper bound on the cost of additional research aimed at reducing this parameter uncertainty. Consequently, this analysis is also an important tool for valuing and guiding research prioritization.

The main advantage of the analysis of the VoI is that it directly addresses the potential implications of current uncertainty, not only in terms of the likelihood of modifying the current decision in light of new and more definitive evidence but also in terms of the opportunity cost of the incorrect decision. If this cost is low, there is little value in agonizing about the decision, even for a low probability of cost-effectiveness, as the implicit penalty is

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negligible if the decision turns out to be wrong in the face of new evidence. Therefore, the probability of cost-effectiveness alone can give an inaccurate representation of decision sensitivity. For this reason, it has been advocated that VoI measures should also be presented when representing decision uncertainty.<sup>11,16-18</sup>

Despite the useful features of a VoI analysis, its uptake in health economic evaluation has been slow. VoI analysis has been hindered by 2 factors in the main. First, the interpretation of the expected value of information is not straightforward as VoI measures are theoretically unbounded, making their assessment challenging.

Second, and perhaps more important, VoI measurements can be computationally costly unless restrictive assumptions are made.<sup>19</sup> Practically, it is easy to calculate the expected value of learning *all* the model parameters numerically (although not analytically). This is known as the (overall) expected value of perfect information (EVPI). However, this has little practical use, as it rarely will be possible to learn *all* the model parameters at once in a new study. Thus, the decision maker is usually interested in the expected value of information about subsets of parameters. This will indicate which parameters are driving decision uncertainty and thus where future research may add value. This subset analysis is called the expected value of perfect partial information (EVPPPI), and it is one of the analyses that is computationally costly. Therefore, significant effort has been invested in developing more efficient methods for computing the EVPPPI.<sup>11,20-25</sup>

A review<sup>26</sup> published in 2008 discussed some of these methods. However, research in this area has been active over the last few years. We therefore present and evaluate the most recent methodological advances in terms of ease of use, accuracy of prediction, and computational time.

We begin by formalizing the EVPPPI calculation and briefly discussing the methods from the previous review. We then present 2 methods for single-parameter EVPPPI before discussing the most recent developments based on nonparametric regression. Then, we compare the performance of these methods using 2 examples of economic modeling. From our analysis, it appears that all methods produce comparable results in the dual decision setting with similar standard errors and computational time. We demonstrate some difficulties in the multiple decision setting along with the computational time required for EVPPPI calculation with larger parameter subsets. Finally, we present some discussion

to suggest that although still affected by some computational limitations, the nonparametric regression methods offer the most suitable EVPPPI approximation method.

## NOTATION AND BASIC CONCEPTS

Health economic decision making aims to determine the optimal intervention with respect to the costs and health effects of several alternative options. Usually, we consider  $t=0$  as the standard intervention currently available for the treatment of a specific condition and  $t=1, \dots, T$  as a (set of) new option(s) being assessed; that is, there are  $T+1$  options in total.

Each alternative  $t=0, \dots, T$  is valued by means of a *utility function*, typically defined in terms of the monetary net benefit

$$nb_t = ke_t - c_t.$$

Here,  $(e_t, c_t)$  is the health economic response, typically subject to individual variability expressed by a joint probability distribution  $p(e, c | \theta)$  indexed by a set of relevant parameters  $\theta$ , while  $k$  is the *willingness to pay*.

In a full Bayesian setting, a complete ranking of the alternatives is obtained by computing the expected value of this utility function, over both individual variability and parameter uncertainty:

$$\mathcal{NB}_t = kE[e_t] - E[c_t],$$

that is, the expectation is taken with respect to the joint distribution  $p(e, c, \theta) = p(e, c | \theta)p(\theta)$ . The option  $t$  associated with the maximum overall expected utility  $\mathcal{NB}^* = \max_t \mathcal{NB}_t$  is deemed to be the most cost-effective, given current evidence.

However, when performing PSA, we simply consider the expected utility taken with respect to individual variability (i.e., as a function of the parameters  $\theta$ ):

$$NB_t(\theta) = kE[e_t | \theta] - E[c_t | \theta],$$

which, in line with Baio,<sup>16</sup> we term the “known-distribution” net benefit. In this case, the expectation is taken with respect to the conditional distribution  $p(e, c | \theta)$ . Thus, while  $\mathcal{NB}_t$  is a deterministic quantity,  $NB_t(\theta)$  is a random variable (with randomness induced by uncertainty in the model parameters  $\theta$ ) and  $E[NB_t(\theta)] = \mathcal{NB}_t$ .

In general, the vector of parameters can be split in 2 components  $\theta = (\phi, \psi)$ , where  $\phi$  is the subvector

of parameters of interest (i.e., those that could be investigated further) and  $\psi$  are the remaining “nuisance” parameters. To calculate the EVPPI, we compute the net benefit for the optimal decision at every point in the support of  $\phi$ , after having marginalized out the uncertainty due to  $\psi$ :

$$\max_t E_{\psi|\phi}[\text{NB}_t(\boldsymbol{\theta})],$$

which is the value of learning  $\phi$  with no uncertainty. Of course, we will never be in the position to completely eliminate the uncertainty on  $\phi$ , so we then average over its current probability distribution while also subtracting the value of the current optimal decision to calculate the EVPPI:

$$\text{EVPPI} = E_{\phi} \left[ \max_t E_{\psi|\phi}[\text{NB}_t(\boldsymbol{\theta})] \right] - \max_t E_{\boldsymbol{\theta}}[\text{NB}_t(\boldsymbol{\theta})]. \quad (1)$$

## REVIEW OF AVAILABLE METHODS FOR THE COMPUTATION OF THE EVPPI IN HEALTH ECONOMIC EVALUATIONS

It is rarely possible to calculate the EVPPI analytically, as the known distribution net benefit is often a complicated function of the underlying parameters. Additionally, it is challenging to calculate the expectation of a maximum analytically, as is required in the first term of Equation 1. For this reason, a wealth of papers have been dedicated to finding accurate approximation methods for the EVPPI.

### EVPPI Approximation Methods Requiring Additional Sampling or Underlying Assumptions

The most recent methodological review of these methods<sup>26</sup> presented 4 approximation procedures for the EVPPI. Two of these methods are computationally intensive and derive directly from the construction of the first term in Equation 1. In the following section, one of the case studies compares the more recently developed methods with the 2-step MC procedure presented by Coyle and Oakley,<sup>26</sup> originally from Brennan and others.<sup>27</sup> This method uses MC sampling to approximate all the expectations in Equation 1. This is computationally intensive, as nested sampling must be used for the first term in Equation 1.

The other 2 methods presented by Coyle and Oakley<sup>26</sup> can only be used when the known-distribution net benefit function fulfills certain

conditions, generally involving some form of linearity in the parameter sets and/or simplifying distributional assumptions. These methods are considerably faster in terms of computational time. Since the publication by Coyle and Oakley,<sup>26</sup> methods have been explored for manipulating models such that they conform to these conditions,<sup>21</sup> thereby reducing the computational time. These methods require an in-depth knowledge of the underlying health economic model and cannot be used for all models. Therefore, they are not evaluated in our review. However, results from Madan and others<sup>21</sup> will be used as a comparator for the second case study.

All of the methods presented by Coyle and Oakley<sup>26</sup> rely on additional information about the model—either to perform more sampling or to check whether it conforms to certain conditions—making EVPPI calculation challenging, both methodologically and computationally. However, since the Coyle and Oakley<sup>26</sup> study was published, significant developments have been made allowing the EVPPI to be calculated quickly using the data already available as part of a standard PSA procedure irrespective of the underlying model structure. Practically, these methods can be easily implemented by practitioners, and thus it is important to ascertain which method should be recommended.

### Approximations for Single-Parameter EVPPI

Recently, 2 methods to approximate the first term of the EVPPI where the interest is in a single-parameter  $\phi$  have been developed. These rely on the following similar ideas:

- A1. If the optimal decision is constant for a certain interval  $\mathcal{I}$  of  $\phi$  values (i.e., it is known that the best treatment is  $t$  when  $\phi$  is contained in  $\mathcal{I}$ ), then the inner conditional expectation in Equation 1 can be approximated by the average known-distribution net benefit value for treatment  $t$ , within  $\mathcal{I}$ .
- A2. If a treatment option is optimal for 1 value of the parameter  $\phi'$ , it is still optimal for parameter values “close to” the point  $\phi'$ .
- A3. There are a *small* number of times that the optimal decision switches between different treatments.

These conditions mean that it is possible to approximate the first term in Equation 1 from a set of  $S$  simulated known-distribution net benefit values for different treatments, provided it is possible to partition these net benefits into sections where

there is some assurance that the optimal decision is constant. These ideas hold irrespective of the correlations between the parameter of interest  $\phi$  and the remaining model parameters.

### Strong and Oakley

The first method for single-parameter EVPPI<sup>24</sup> is based on the idea that if the parameter space is split into “small” subsets, the optimal decision is unlikely to change within each subset (Assumption A2), as it is reasonable to assume it is locally constant. This in turn allows the use of Assumption A1 to calculate the maximum expected net benefit for each  $\phi$  value.

Thus, to calculate the EVPPI, it is necessary to determine subsets of the simulated values of  $\text{NB}_t(\boldsymbol{\theta})$  for which the simulated values of  $\phi$  are similar. Practically, this is achieved by reordering the “observed” known-distribution net benefit values so that they have the same order as the simulated values for  $\phi$ —note that since it is assumed that  $\phi$  is a scalar, ordering is trivial. This list of ordered values is then split into  $M$  small sublists of length  $L = \frac{S}{M}$ . Within each sublist, the average known-distribution net benefit is calculated for each treatment option, and the maximum within each subset is used as an estimate for the first term in Equation 1.

Therefore, the following strategy can be used:

1. Sample  $S$  values from the distribution of the parameters  $\boldsymbol{\theta}$ ; we indicate these as  $\boldsymbol{\theta}^1, \dots, \boldsymbol{\theta}^S$ .
2. At each iteration  $s=1, \dots, S$ , use the simulated parameter vector  $\boldsymbol{\theta}^s$  to compute the estimated known-distribution net benefit  $\text{NB}_t(\boldsymbol{\theta}^s)$  for each treatment option  $t$ .
3. Sort the simulated values of the parameter of interest in ascending order—for simplicity, we write the sorted vector as  $\varphi^1, \dots, \varphi^S$ , where  $\min\phi = \varphi^1 < \dots < \varphi^S = \max\phi$ .
4. Reorder the estimated known-distribution net benefits as  $\text{NB}_t(\varphi^1), \dots, \text{NB}_t(\varphi^S)$ , where  $\text{NB}_t(\varphi^s)$  is the net benefit corresponding to the  $s$ -th ordered simulated value of  $\phi$ .
5. Split the ordered list of known-distribution net benefits into  $m=1, \dots, M$  sublists  $\mathcal{L}_m$  of length  $L$  and compute the average in each sublist for each treatment  $t$  to obtain  $\widehat{\text{NB}}_t^m(\boldsymbol{\theta}) = \frac{1}{L} \sum_{j \in \mathcal{L}_m} \text{NB}_t(\varphi^j)$ .

6. Compute  $\widehat{\text{EVPPI}} = \frac{1}{M} \sum_{m=1}^M \max_t \widehat{\text{NB}}_t^m(\boldsymbol{\theta})$ .

The approximation given by this method is highly sensitive to the value of  $M$ . If  $M$  is small, the EVPPI is approximately 0, giving a downwardly biased estimate. At the other end of the scale, when  $M$  is large, the EVPPI is close to the overall EVPI estimate, giving an upwardly biased estimate. To find an appropriate  $M$ , Strong and Oakley<sup>24</sup> suggest using a multivariate normal approximation to estimate this upward bias. They then suggest choosing  $M$  to be the largest number of subsets such that the upward bias falls below a prespecified threshold value. In this manner, the upward bias of the EVPPI estimate, present when the chosen value of  $M$  is too large, is controlled while the downward bias, present for small values of  $M$ , is likely to be avoided. A full explanation of this bias estimation method, along with relevant R code, is given in the supplementary material.

### Sadatsafavi and Others

This second method<sup>23</sup> can be thought of as an extension of the previous one, although both were developed concurrently. In this case, the ordered list

$$\mathbf{NB}(\boldsymbol{\theta}) = \begin{pmatrix} \text{NB}_0(\varphi^1) & \dots & \text{NB}_0(\varphi^S) \\ \text{NB}_1(\varphi^1) & \dots & \text{NB}_1(\varphi^S) \\ \vdots & \vdots & \vdots \\ \text{NB}_T(\varphi^1) & \dots & \text{NB}_T(\varphi^S) \end{pmatrix}$$

is split in an informed manner. The algorithm searches for the point(s) at which the parameter of interest is responsible for a change in the optimal decision. Although, in general, variations in a parameter may induce a change in the optimal decision a large number  $M$  of times, in practice a single parameter is unlikely to modify it more than once or twice over the range of values selected for the willingness-to-pay. Provided we search for the correct number of decision changes, the method calculates the true EVPPI values, asymptotically as the number of PSA samples goes to infinity.

The algorithm developed by Sadatsafavi and others is identical to that of Strong and Oakley described in the previous section in Steps 1–4 but then proceeds as follows:

5. Split the ordered list of net benefits into  $m=1, \dots, M$  sublists  $\mathcal{L}_m$ . In this case, the list of known-distribution net benefit values is split at  $M$  points,  $(\varphi^{\mathcal{L}_1}, \dots, \varphi^{\mathcal{L}_M})$ , known as the *segmentation vector*. This means that the  $m$ -th sublist

contains all the net benefit values calculated with the value  $\varphi$  such that  $\varphi^{\mathcal{L}_m} \leq \varphi < \varphi^{\mathcal{L}_{m+1}}$ .

6. Calculate and store  $\widehat{NB}_t^m(\boldsymbol{\theta}) = \frac{1}{L} \sum_{j \in \mathcal{L}_m} NB_t(\varphi^j)$ .
7. Maximize over all possible segmentation vectors to compute  $\widehat{EVPPI} = \max_{(\varphi^{\mathcal{L}_1}, \dots, \varphi^{\mathcal{L}_M})} \frac{1}{M} \sum_{m=1}^M \max_t \widehat{NB}_t^m(\boldsymbol{\theta})$ .

As the properties of the EVPPI estimate are dependent on searching for the correct number of decision changes  $M$ , Sadatsafavi and others suggest a systematic method for choosing  $M$ , based on a visual tool for determining the number of decision changes. This tool plots the cumulative sum of the differences between the known-distribution net benefits for 2 treatment options, ordered in the parameter of interest  $\phi$ . When the optimal decision changes, so does the sign of the difference between the 2 treatment options. Thus, a change in optimal decision is shown by a maximum or minimum for this cumulative sum. An example of this visual tool is given in the supplementary material.

Correctly identifying the number of decision changes is vital. This is clearest when the EVPPI is 0: that is, when the parameter  $\phi$  does not affect the optimal decision. In this case,  $M=0$ ; however, choosing  $M=1$  will give an EVPPI estimate that is strictly positive and therefore upwardly biased. If the correct number of decision changes is used, then the EVPPI estimate is asymptotically unbiased. However, as demonstrated in the supplementary material, it can be challenging to determine extrema, possibly making the EVPPI estimate inaccurate.

Both these single-parameter estimation methods are dependent on their inputs, making “black-box” calculations difficult. In addition, since the publication of these 2 methods, further research has allowed for the calculation of multiparameter EVPPI using the PSA samples and nonparametric regression methods.

### Nonparametric Regression for EVPPI Calculations

The basic idea proposed initially by Oakley<sup>22</sup> and developed further by Strong and others<sup>25</sup> is that regression methods can be used to approximate the EVPPI. Specifically, Strong and others<sup>25</sup> demonstrate that the inner conditional expectation in Equation 1 can be approximated, using the sampled parameter values  $\phi^s$ , which will usually be available when performing PSA. In particular, since health economic models are likely to be complicated functions of the

underlying parameters, flexible regression methods should be used, to limit the number of assumptions on the relationship between the inner conditional expectation and the parameters.

For each simulated value of the parameters, Strong and others propose to approximate the inner conditional expectation as

$$NB_t(\boldsymbol{\theta}^s) = E_{\psi|\phi^s} [NB_t(\phi^s, \psi^s)] + \epsilon^s,$$

with  $\epsilon^s \sim \text{Normal}(0, \sigma_\epsilon^2)$  and where  $\boldsymbol{\theta} = (\phi, \psi)$ . Furthermore, conditional expectation can be thought of as a function of  $\phi$ , as it is dependent on the value of  $\phi$ . Therefore, the problem can be formulated in terms of regression equation:

$$NB_t(\boldsymbol{\theta}^s) = g_t(\phi^s) + \epsilon^s,$$

for which  $\phi^s$  are “observed” values (obtained via MC sampling) of the independent variables and  $NB_t(\boldsymbol{\theta}^s)$  is the “observed” dependent variable. It is important to note that this method works irrespective of the relationship between  $\phi$  and  $\psi$ ; there is no need for these parameter sets to be uncorrelated or independent.

Strong and others<sup>25</sup> provide R code<sup>28</sup> for 2 alternative nonparametric regression methods: generalized additive models (GAMs)<sup>29</sup> and Gaussian processes (GPs).<sup>30</sup> GAMs model the net benefit as a sum of “smooth” functions of the parameters  $\phi$ . These smooth functions are built up using polynomials and are characterized by a large number of “regression” parameters. Therefore, GAM regression becomes infeasible as the size of  $\phi$  increases because the number of “regression” parameters increases exponentially and will therefore exceed the number of observations of the known-distribution net benefit  $S$ . GPs are a flexible regression method based on the multivariate normal distribution. GPs introduce flexibility by modeling the covariance matrix of the known-distribution net benefits dependent on the  $\phi$  values and some hyperparameters that must be estimated. This hyperparameter estimation can be computationally costly for larger values of  $S$ . These flexible regression methods allow the conditional expectation to be estimated correctly, but other regression methods could be used. In a general sense, the EVPPI estimate is calculated by means of the following algorithm:

1. Sample  $S$  values  $(\boldsymbol{\theta}^1, \dots, \boldsymbol{\theta}^S)$  from the distribution of the parameters.

2. Calculate the net benefit  $NB_t(\theta^s)$  for each observed parameter vector  $\theta^s$  and treatment option  $t$ .
3. For each treatment option  $t$ , fit a regression curve with  $\phi^s$  as the observed “covariates” and  $NB_t(\theta^s)$  as the observed “dependent” variable, for the  $s$ -th “unit” of analysis (i.e., simulation).
4. For each treatment  $t$ , estimate  $E_{\psi|\phi^s}[NB_t(\phi^s, \psi)]$  using the  $s$ -th fitted values  $g_t(\phi^s)$  obtained by inputting the observed values  $\phi^s$  into the regression curves.
5. Calculate

$$\widehat{EVPPI} = \frac{1}{S} \sum_{s=1}^S \max_t g_t(\phi^s) - \max_t \frac{1}{S} \sum_{s=1}^S g_t(\phi^s).$$

This nonparametric regression method was published most recently and thus represents the current state of the research into estimation methods for the EVPPI. However, despite the relative complexity of this method, “black-box” calculations are possible using standard “regression” forms for the GAM methods and conjugate prior distributions for the GP requiring little to no input from the user. This allows for the creation of general purpose functions<sup>28</sup> and the web application Sheffield Accelerated Value of Information (SAVI)<sup>31</sup> to aid users to calculate EVPPI. This web application also produces standardized output, graphics, and tables that can be easily presented in formal reports. All these methods are also implemented in the R package BCEA.<sup>32,33</sup>

As this method is based on nonparametric regression, standard methods, such as qq-plots and residual plots, should be used to check the model fit. If this model fit is bad (e.g., as shown by structure in the residual plots such as an S- or U-shape), then it is likely that the EVPPI is poorly estimated. This is because the regression fit has not picked up all the structure due to  $\phi$  and so the EVPPI will be biased.<sup>34</sup>

## COMPARISON OF METHODS

This section compares the EVPPI estimates given by the methods discussed in this review with a MC procedure for 2 different case studies. To begin, the case studies are presented, one pertaining to influenza infection vaccination and the other to fluid resuscitation for malaria. We then discuss how the EVPPI estimates were calculated with regard to the input values for the single-parameter methods. We also discuss how the estimation methods can be extended to multiparameter, multidecision settings. Finally, we present the EVPPI estimates for a large

number of different parameter sets for both cases studies, along with the standard error and computational time required to obtain these estimates.

Because all these EVPPI calculation methods are simply based on the PSA samples obtained from the underlying statistical models, it is unlikely that the estimation methods are affected by the structure of the model. Thus, the following examples can be thought of as illustrative and the conclusions extended to other health economic models. We do note, however, that these case studies represent relatively complex standard health economic models. This should ensure that the success or otherwise of the methods we present is not related to the simplicity of the underlying model structures.

## Case Studies

### *Influenza Vaccine*

A Bayesian health economic model synthesizing information from several sources is proposed to analyze the effect of the influenza vaccine on health-outcomes and costs. This example is relatively simple but complex enough for the posterior distribution to be intractable analytically. Therefore, the parameter values must be sampled from their joint posterior distribution using Markov chain Monte Carlo (MCMC) methods. Updating the joint posterior may induce correlations for parameters that are independent a priori, meaning that the dependence structure of the parameters is not known.

Two treatment options are considered, either the vaccine is available to the population ( $t=1$ ) or not ( $t=0$ ). If a patient gets influenza, he or she is treated with antiviral drugs and will often visit a primary care practitioner. Complications may occur, including pneumonia and hospitalization, in which case there will be some indirect costs such as time off work. The cost of the treatment is the acquisition cost of the drugs, the time in hospital, the primary care visits, and the cost of the vaccine. The benefit of the treatment is measured in quality-adjusted life-years (QALYs), where each adverse effect contributes negatively to the benefit.

The model contains 28 key parameters representing the probability of infection, the reduction in risk due to the vaccine, the occurrence of complications, the monetary costs of the interventions, and the QALY loss due to different health states. A detailed discussion of the full model parameterization is presented in Baio and Dawid,<sup>35</sup> based on Cooper and others.<sup>36</sup> The single-parameter EVPPI was calculated

for all of these 28 parameters using all the methods outlined.

### **FEAST Trial**

This example pertains to a trial for fluid resuscitation in the treatment of malaria.<sup>21</sup> This is a decision tree model where both the probabilities of progression as well as the QALYs and costs are estimated from various sources. The parameters in this setting are either estimated using Bayesian updating based on a set of randomized controlled trials or sampled directly from an informed prior distribution. Therefore, in this example, the independence structure of some of the parameters is known. The example has 4 potential treatment options, 3 different fluids, and a standard of care arm.

The use of fluids is aimed at reducing the number of patients living with long-term neurological sequelae (NS) along with the risk of death. Living with long-term health complications has an added financial cost and loss in QALYs. This model has 9 parameters and is used to test the method proposed by Madan and others.<sup>21</sup> Therefore, the MC EVPPI values used in this paper as the “truth” are taken directly from Madan and others.<sup>21</sup>

For each active intervention  $i=1,2,3$ , the parameters in this case study represent the effect of the different fluids on mortality,  $d_i^M$ ; and on the NS risk,  $d^S$  (which is assumed constant across the fluids); the log-odds of death without fluids,  $\alpha$ ; the probability of NS at 28 days,  $p^B$  and 6 months,  $p^L$ ; and the QALY loss per fatality,  $q^M$  and per case of NS,  $q^S$ .

### **Analysis**

#### **Influenza Vaccine**

This analysis compares the methods presented by estimating single-parameter EVPPI, as some of the methods are only suitable in such cases. As previously discussed, both single-parameter estimation methods have input values that greatly affect the estimation. Therefore, to determine these values, the suggested visual tool was used for each of the 28 parameters in the vaccine case study.\* It was decided that 23 of the 28 parameters change the optimal decision once as one extremum was

identified; the other parameters have no effect—these correspond to an EVPPI equal to 0 in Table 1. In these cases, the visual tool was judged to be strictly increasing or decreasing. This can be difficult to ascertain as the visual tool does not give smooth curves, as can be seen in the supplementary material, because the PSA data are noisy.

For the Strong and Oakley<sup>24</sup> method, the upward bias of the EVPPI estimate was assessed for all the parameters in the data set. The number of subsets was taken as the largest number of subsets such that the upward bias standardized by the EVPI value remains below 0.04, although other thresholds may give equally good estimates. The magnitude of the bias differed for each parameter, and therefore the number of subsets needed to reduce the standardized upward bias below 0.04 was between 20 and 2. A larger number of subsets is associated with a larger estimate for the EVPPI, and so it is important to assess the correct number of subsets for each parameter individually.

For the 2-step MC procedure, the outer loop had 1000 observed posterior samples for all the parameters. As the case study is a Bayesian model with an analytically intractable posterior distribution, the inner loop of the 2-step MC procedure used MCMC methods to draw a sample from this joint posterior distribution for all the parameters. To ensure convergence and reduce autocorrelation, we took 2 chains of 100,000 samples each for the inner loop, with a burn-in of 9500 and thinning of 500. Therefore, the eventual sample of the known-distribution net benefits had 1000 observations. The MC error on this estimate is still quite large, around 10%–30% of the underlying EVPPI value; ideally we would have sampled more observations in the inner loop. This was, however, an infeasible computational burden. To calculate the value of the current information, we sampled from our MCMC procedure 50,000,000 times, with a burn-in of 9500, and then thinned to 500,000. This sample size gives a MC error on the estimate for the current information around 0.009 for an estimate of current information of 0.041. As only 2 treatment options are considered, the incremental net benefit was stored for each loop, and the maximum between the stored value and 0 was found.

Finally, the 2 nonparametric regression methods suggested by Strong and others<sup>25</sup> were used to calculate the EVPPI by approximating the inner expectation in Equation 1. This analysis was carried out using the functions in Strong.<sup>28</sup> For GAM regression, the functions use spline regression as

\*The supplementary material gives a more in-depth explanation of this visual tool and gives an example of the tool using some of the parameters from the Vaccine example.

**Table 1** Expected Value of Partial Perfect Information for the Vaccine Example

Parameter		Methods					
		SO	SAD	GP	GAM	MC	
Probability of clinical outcomes	$\beta_1$	1.15 (0.11)	1.17 (0.11)	1.11 (0.13)	1.11 (0.12)	1.06	
	$\beta_2$	0.26 (0.1)	0.23 (0.1)	0.11 (0.12)	0.11 (0.1)	0.25	
	$\beta_3$	0.24 (0.09)	0.15 (0.06)	0.03 (0.03)	0.03 (0.02)	0.08	
	$\beta_4$	0.14 (0.1)	0.13 (0.06)	0.08 (0.03)	0.09 (0.04)	0.06	
	$\beta_5$	0.28 (0.1)	0.25 (0)	0.07 (0.02)	0.12 (0.02)	0.07	
	$\beta_6$	0.27 (0.1)	0.29 (0)	0.18 (0.1)	0.21 (0.1)	0.22	
	$\beta_7$	0.35 (0.1)	0.4 (0.1)	0.3 (0.08)	0.3 (0.08)	0.25	
Number of drugs prescribed	$\delta$	0.3 (0.11)	0.22 (0.06)	0.11 (0.03)	0.03 (0.02)	0.06	
Probability of taking time off work	$\eta$	0.11 (0.1)	0 (0)	0.04 (0.02)	0 (0.02)	0.09	
Probability of receiving drugs	$\gamma_1$	0.19 (0.08)	0.17 (0.06)	0.11 (0.02)	0.11 (0.02)	0.07	
	$\gamma_2$	0 (0.1)	0 (0)	0.01 (0.02)	0.01 (0.02)	0.06	
Number of days off work	$\lambda$	0.41 (0.1)	0.44 (0.1)	0.41 (0.1)	0.43 (0.1)	0.43	
Reduction in infection rate due to vaccine	$\rho$	0.3 (0.1)	0.3 (0.06)	0.28 (0.08)	0.28 (0.08)	0.28	
Probability of taking OTC medication	$\xi$	0.24 (0.09)	0.13 (0.11)	0.03 (0.02)	0.03 (0.02)	0.06	
QALY cost for each state	$\omega_1$	0.55 (0.11)	0.57 (0.06)	0.53 (0.13)	0.53 (0.12)	0.63	
	$\omega_4$	0.2 (0.09)	0.23 (0)	0 (0.02)	0 (0.02)	0.07	
	$\omega_5$	0.11 (0.1)	0.17 (0)	0.05 (0.02)	0.05 (0.02)	0.06	
	$\omega_6$	0.18 (0.1)	0.16 (0)	0.12 (0.08)	0.12 (0.07)	0.13	
	$\omega_7$	0.18 (0.1)	0.29 (0)	0.14 (0.06)	0.16 (0.06)	0.15	
	Vaccine coverage rate	$\phi$	0.13 (0.09)	0 (0)	0.02 (0.03)	0.02 (0.04)	0.06
	Cost of resources	$\psi_1$	0.17 (0.09)	0.17 (0)	0.13 (0.03)	0.13 (0.02)	0.07
		$\psi_2$	0.1 (0.08)	0.14 (0)	0.02 (0.02)	0.02 (0.02)	0.07
$\psi_3$		0.37 (0.1)	0.37 (0.11)	0.31 (0.09)	0.31 (0.09)	0.29	
$\psi_4$		0.46 (0.11)	0.52 (0.1)	0.35 (0.07)	0.35 (0.07)	0.42	
$\psi_5$		0.44 (0.11)	0.38 (0.06)	0.24 (0.06)	0.38 (0.06)	0.25	
$\psi_6$		0.13 (0.11)	0.15 (0)	0.05 (0.02)	0.05 (0.01)	0.07	
$\psi_7$		0.2 (0.1)	0 (0)	0 (0.05)	0 (0.05)	0.07	
$\psi_8$		0.08 (0.08)	0 (0)	0 (0.04)	0 (0.04)	0.07	

Note: Values in British pounds (£), standard error in parenthesis. SO, Strong and Oakley single parameter estimation; SAD, Sadatsafavi et al. single parameter estimation; GP, Gaussian process; GAM, generalized additive model regression; MC, two-step Monte Carlo simulation.

smoothing functions. The R function `gam` is used by Strong<sup>28</sup> to fit the spline regression, and `gam` chooses the dimension of the underlying basis functions. Therefore, no additional input is needed for single-parameter GAM regression. For GPs, Strong and others use a specific model structure to make use of analytical results so no specific model structure is needed and functions are provided to calculate the EVPPI with no additional inputs.

### FEAST Trial

This analysis compares the performance of the different EVPPI estimation methods for all the subsets considered by Madan and others.<sup>21</sup> There are 12 different parameter subsets considered, of which

3 contain more than 1 parameter. Therefore, this example assesses the performance of the multiparameter EVPPI calculation methods as well as the single-parameter methods in a multidecision setting. All the analyses performed in this section were performed on 5 million samples from the FEAST analysis performed by Madan and others. This was thinned to 1000 to reduce the substantial autocorrelation in the sample and the computational times.

The methods require some simple extensions for multidecision/multiparameter problems. To extend the nonparametric regression methods to multidecision models, a regression curve must be fitted per *incremental* decision (i.e., 3 in this example). This adds little complexity for the investigator, as code to fit regression will already be available; however, it

can increase the computational time. As the GAM regression becomes infeasible for “large” parameter subsets, the GP regression is the only option for 2 of the 3 multiparameter EVPPI calculations. For this method, we use 500 PSA samples to estimate the hyperparameters, the default option. For the multiparameter GAM method, we model full interactions.

For the single-parameter methods, the input values must be determined. To use Sadatsafavi and others<sup>23</sup> method for multidecision problems, it is necessary to decide how many decision changes there are for each pair of decisions. Therefore, in this setting we have to consider the visual tool for 6 different pairs of decisions. This decreases the accuracy of the method as the visual tool can be difficult to interpret and, therefore, with 6 decisions per EVPPI calculation, the possibility of an error is greater. In this case, the number of decision changes between pairs of decisions varied between 0 and 3.

For the Strong and Oakley<sup>24</sup> method, the bias reduction technique was used. In this setting, the number of blocks was relatively small for all EVPPI calculations, varying between 5 and 2. These values were determined by insisting that the upward bias for the EVPPI standardized by the EVPI had to fall below 0.02. This threshold is slightly lower than for the vaccine example, as a standardized threshold of 0.04 represents an absolute upward bias of around \$22, which is high when the EVPPI is close to 0.

All the analyses in this paper were run using R (version 3.2.1). The MCMC simulations were run using JAGS, which was called using the R package rjags. Computations were performed on a PC with an Intel i7 processor and 8Gb of RAM.

## Results

Table 1 displays the single-parameter EVPPI estimates for the 5 different methods for the vaccine example. All the methods give approximately the same results for each parameter. The 2 parameters with the highest EVPPI are the same across all 5 methods:  $\beta_1$  and  $\omega_1$ , representing respectively the probability and QALY cost of an influenza infection. Although there is some discrepancy in the ordering, the results only differ slightly, certainly in comparison to the MC error of the current information, which is 0.009.

Supplementary Table S1 gives the EVPPI for all the parameter sets in the FEAST example. For this example, the method by Sadatsafavi and others

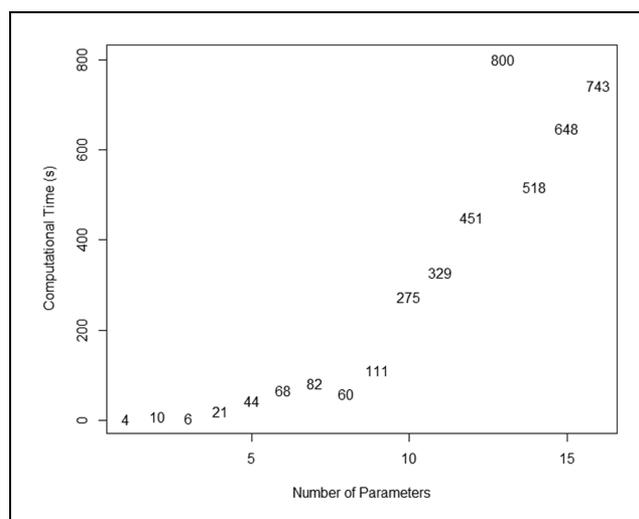


Figure 1 The computational time required for EVPPI estimation for the GP regression method, varying with the number of parameters for which the EVPPI is begin calculated.

struggles to retrieve the true EVPPI. This is due to the difficulty in ascertaining the number of decision changes for each pair for decisions. The other methods give similar answers across all the different parameter sets, with some difficulties with the Strong and Oakley method and the GP regression for  $d_3^M$  and  $d_4^M$  (representing the effect of the saline and gelofusine fluids on mortality, respectively) and for the GAM regression for the parameter subset of size 4, where the estimate is more than 1 standard error away from the MC “truth.”

To compare the different methods, the computational time required to produce the estimate was investigated. For the vaccine example, the single-parameter estimation methods and the GAM regression took fewer than 0.01 seconds to find single-parameter EVPPI estimates. In contrast, the GP regression takes between 2 and 4 seconds, which is still fast in comparison to the MC procedure, which takes around 55 minutes to calculate a single-parameter EVPPI estimate.

For the FEAST example, the single-parameter estimation times are similar, although the GP method increased for this example to 7–9 seconds as hyperparameters need to be estimated for each (incremental) decision. The multiparameter estimation times are significantly longer. In the 4-parameter example, the GP method took 85 seconds, while the GAM regression method took 184 seconds. Madan and others<sup>21</sup> give the 1-step MC estimation time as 84 seconds while the 2-step MC is

31 minutes. For the 7-parameter examples, the GP regression times are 229 and 279 seconds, respectively, while Madan and others give the estimation times as 9 and 10 seconds for single-step and 26 minutes for 2-step MC.

The standard error for the EVPPI estimate were also calculated to allow the methods to be compared. Table 1 shows the standard error given in brackets for all the methods (excluding the Monte-Carlo procedure) for the vaccine example. The standard error is similar across all 4 methods for all parameters and also decreases as the EVPPI estimate decreases. For the FEAST example, Supplementary Table S1, the standard error (given in brackets) is broadly consistent across the different methods. Again, the larger the EVPPI estimate, the larger the estimated standard error with a range across different parameter sets of between 10 and 25. This implies that the relative certainty of the EVPPI estimate increases as the estimate itself increases; an EVPPI estimate close to 0 has a standard error of 10, while an EVPPI estimate of 232 only has a standard error of 25.

### Computational Time

To investigate the computational time required for the multiparameter EVPPI estimation methods, the EVPPI was calculated for increasing subsets for the vaccine example. The computational time was taken for subsets containing between 1 and 16 parameters for the GP regression method. The computational times for the GAM regression were also taken for subsets containing between 1 and 4 parameters. This is because the GAM method approximates the EVPPI using a large number of “regression” parameters and, therefore, modeling full interactions forces the number of regression parameters to exceed the number of data points for larger numbers of parameters of interest.

The computational times required to calculate the EVPPI via GAM regression are 0.13, 0.11, 0.66, and 122 seconds for increasing subsets. The computational times for the GP regression are given in Figure 1. Clearly, the greater the number of parameters of interest, the greater the computational time required to calculate the estimate. Additionally, note that the computational time does not increase linearly with the number of parameters but increases exponentially. The computational cost of the GP method is also dependent on the PSA sample size  $S$ , as it is proportional to  $S^3$ .<sup>25</sup>

To tackle these issues, a recent extension to the standard GP regression approach exploiting results from the geostatistics literature has been developed.<sup>37</sup> This method is promising in terms of both accuracy and reduced computational time, with computational time remaining constant as the number of parameters increases.

### Comparison with SAVI

The analyses in this paper were performed using the stand-alone R functions provided by Strong.<sup>28</sup> The SAVI web app, which is the tool currently recommended by the UK National Institute for Health Research (NIHR) for EVPPI calculation, is also based on these functions and therefore should give comparable results. SAVI uses GAM regression for subsets with fewer than 6 parameters and GP regression for larger subsets.

Therefore, the SAVI results should be the same for the single-parameter and 4-parameter EVPPI. For the single-parameter EVPPI, the results are similar but SAVI uses a slightly different formulation which gives values generally further from the MC “truth.” There is a large discrepancy for the 4-parameter EVPPI with an estimate of 365. This is within 1 standard error of the true EVPPI value. This is because SAVI automatically restricts the number of GAM parameters for larger parameter subsets, which in turn reduces computation time and can also prevent overfitting.

For GP regression, the SAVI web app only uses 250 observations<sup>†</sup> to estimate the hyperparameters, whereas the analysis in this paper used 500. This leads to a much increased computation time (around 8 times slower) but greater accuracy. In more complex models, this number of observations may not be sufficient to estimate the hyperparameters, which can lead to inaccuracies in the EVPPI estimation. Therefore, the SAVI web app should be used with care in these settings.

### DISCUSSION

This paper presents the current methods developed for approximating the EVPPI. It particularly focuses on 4 general purpose EVPPI estimation methods that have been developed since an earlier

<sup>†</sup>For large parameter subsets, the number of observations used is 30 multiplied by the number of parameters to prevent overfitting.

review paper.<sup>26</sup> We compared the estimation properties of these 4 estimation methods taking into the account accuracy, when compared with a MC estimator for the true EVPPI values, standard error, computational time, and ease of implementation.

To begin, the method of Sadatsafavi and others<sup>23</sup> is inaccurate for multidecision problems due to difficulties in ascertaining the inputs required for accurate estimation using this method. Therefore, it should be avoided in multidecision settings. For models with only 2 treatment options, this method gave consistent results when compared with the “true” EVPPI and can therefore be used. In terms of standard error and computational time, it is comparable with the other methods but is more challenging to implement than the methods based on nonparametric regression as the number of decision changes needs to be determined using the visual tool. Additionally, it is only applicable to single-parameter EVPPI estimation.

The Strong and Oakley<sup>24</sup> method is accurate in both single- and multidecision settings. It is also comparable in terms of standard error and computational time with the GAM regression method. However, as with the Sadatsafavi and others<sup>23</sup> method, the Strong and Oakley method is applicable only to single-parameter EVPPI estimation and relies heavily on the number of subsets determined using bias reduction, which limits its applicability. In fact, choosing an incorrect input value can lead the researcher to drastically over- or underestimate the EVPPI.

Therefore, due to the ease of implementation, we suggest using the nonparametric regression method for single-parameter and multiparameter EVPPI in all decision models, as these methods are also comparable in terms of accuracy and standard error with the 2 single-parameter methods. Due to the nature of these methods, stand-alone functions,<sup>28</sup> R packages,<sup>33</sup> and web-applications<sup>31</sup> have been developed that allow the user to calculate the EVPPI with minimal input.

These 2 nonparametric regression methods can be compared head-to-head in terms of computational time and accuracy, which leads us to change our recommended method dependent on the number of parameters of interest  $\phi$ . The GAM regression method is suited for parameter subsets containing fewer than 4 parameters as the computational time is negligible and the accuracy is high. However, as the number of parameters of interest increases, the GAM method becomes both less accurate and slower to compute than the GP regression. Additionally, GAM regression is unstable for larger subsets of parameters

(greater than 6)<sup>25</sup> and therefore cannot be used to approximate the EVPPI.

For larger parameter subsets (e.g., greater than 4), GP regression is currently the best available general purpose method. Unfortunately, the GP method takes substantially more computational time as the number of parameters increases, and there is a tradeoff between the computational time spent fitting the model and the accuracy of the EVPPI estimate, specifically when the number of parameter of interest is high. The computational time required to calculate the EVPPI using GP regression method is proportional to  $S^3$ , where  $S$  is the PSA sample size. Therefore, the computational time required to calculate the EVPPI remains high for large-parameter subsets coupled with large PSA samples. We note, however, that the most recent developments reported by Heath and others<sup>37</sup> offer an alternative to GP regression that is both fast and accurate for large parameter subsets.

In addition to these general purpose methods, it must be noted that the Madan and others<sup>21</sup> method is competitive in terms of computational time for model structures where it can be used. However, as it is not a general purpose method, it was outside the scope of our analysis.

In conclusion, recent advances in the computation of the EVPPI have significantly reduced the computational time required to calculate the EVPPI. Additionally, as the methods presented are general purpose and based on only the PSA samples, these methods can be applied by researchers wishing to harness the power of VoI analysis in their analysis. The recommended methods are based on nonparametric regression and can be used in a “black-box” sense using suitable software,<sup>33</sup> SAVI,<sup>31</sup> and code provided by Strong and others.<sup>28</sup> In general, this implies that the computational and methodological barriers to calculating the EVPPI have been broken and these methods can now be recommended to practitioners.

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